REMARKS

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Rejoinder of Claims

Applicants continue to request the rejoinder of claims 8, 9, 18, and 19 directed to methods of making and using the claimed polypeptides upon allowance of a product claim per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103 (b)" which sets forth the rules, upon allowance of product claims, for the rejoinder of process claims covering the same scope of products. Therefore, since it appears a product claim will be allowed, Applicants respectfully request rejoinder and examination of method claims 8, 9, 18, and 19.

Amendments to the Claims

In the interest of expediting prosecution and not for reasons related to patentability, claims 1 and 16 have been amended. Claims 1 b) and 1 c) have been amended to include the recitation of, "said polypeptide retaining at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1." Support for these amendments can be found for example on page 5, lines 25-26 and in review of the specification as a whole the applicants intend that both the variants and biologically active fragments of SEQ ID NO:1 retain at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1. The contents of claim 1 d) which recites, *inter alia*, "an immunogenic fragment" of SEQ ID NO:1 has been deleted. Claim 16 has been amended to remove recitation of "an acceptable excipient." Therefore, entry of these amendments are deemed proper and are respectfully requested.

Rejection under 35 U.S.C.§101, first paragraph

The rejection of claims 1, 2 16 and 17 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

Applicants traverse this rejection for the reasons submitted below.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q.

327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Applicants have established that one skilled in the art would understand that there is a "well-established" utility for the claimed invention

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. The uses of NHT for toxicology testing, drug discovery, and disease diagnosis are practical uses

that confer "specific benefits" to the public. The uses of the claimed polypeptide for gene expression monitoring applications including toxicology testing are in fact independent of its precise function. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

A. The Precise Biological Role Or Function Of An Expressed Polypeptide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Furness Declaration (at, *e.g.*, ¶¶ 10-13), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person

of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed polypeptide, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. The use of proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease are "well-established" utilities for the claimed invention

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (Reference No. 1):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Reference No. 1)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, *et al.*, Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-

159 (1999) (Reference No. 2); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (Reference No. 3).

The more genes – and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See email from the primary investigator of the Nuwaysir paper, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 4) Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Accordingly, the use of the claimed invention, even without knowing its precise biological role or function has a well-established utility through its use as a tool for toxicology testing, drug discovery or the diagnosis of a disease.

C. The Furness Declaration is submitted in support of "well-established" utilities of NHT, and thus, at least one utility for SEQ ID NO:1

The Declaration of Lars Michael Furness presents objective evidence of at least one well-established utility for the claimed invention. The Furness Declaration describes some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood by one of skill in the art at the time of the patent application.

The Furness Declaration is submitted to corroborate Applicants' established, real world utility for the instant invention in toxicology testing, disease diagnosis and drug development. The Furness Declaration explains the many reasons why the claimed polypeptides and compositions have utilities in toxicology testing and drug discovery regardless of knowing the biological function of the claimed polypeptide, and that these utilities would have been understood by one of skill in the art who read the LaBrie '824 application on or before March 6, 1997. As stated by Mr. Furness on page 3; ¶ 5 of the Furness Declaration:

> I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner's position that the LaBrie '390 application and its parent, the LaBrie '824 application, does not disclose a substantial, specific and credible "real-world" utility for the claimed SEQ ID NO:1 polypeptide, and (b) to state and explain the bases for any conclusions I reach.

In his Declaration, Mr. Furness describes how a person skilled in the art on March 6, 1997 would have understood the LaBrie '824 application to disclose the claimed polypeptide to be useful for a number of gene and protein expression monitoring applications. In particular, how the claimed polypeptide can be used in protein expression analysis techniques such as 2-D PAGE technologies and western blots in connection with the development of drugs and the

monitoring of the activity and the potential toxic effect of such drug candidates. (Furness Declaration at, e.g., ¶¶ 11-14).

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.*, in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. (Furness Declaration at ¶ 11.)

Much, but not all, of Mr. Furness' explanation concerns the use of the claimed polypeptide in the creation of protein expression maps using 2-D PAGE. The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

> In view of the LaBrie '824 application, the Wilkins article, and other related pre-March 6, 1997 publications, persons skilled in the art on March 6, 1997 clearly would have understood the LaBrie '824 application to disclose the SEQ ID NO:1 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 12 below. (Furness Declaration, ¶ 10)
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> * * *
>
> Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:1 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating appetite and eating disorders, especially anorexia, cachexia and obesity for such purposes as evaluating their efficacy and toxicity. (Furness Declaration, ¶ 12)

Mr. Furness' observations are confirmed in the literature published before the filing of the patent application. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, for the basis of two-dimensional gel databases. (Wilkins, Tab C, p. 26).

Therefore, the Furness Declaration provides objective evidence that a person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide in the absence of any knowledge as to the precise function of the protein. The uses of the claimed polypeptide for gene expression monitoring applications including toxicology testing are in fact independent of its precise function. Thus, the use of the claimed invention in 2-D PAGE gels and western blots to assess expression and toxicity of SEQ ID NO:1 are "real-world" utilities which are credible, specific and substantial utilities attributable to the claimed invention.

D. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), **in particular genes having medical and pharmaceutical significance such as the instant sequence**. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other

sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polypeptide, the databases become even more powerful tools. Thus, the claimed invention adds more than incremental benefit to the drug discovery and development process.

E. The uses of NHT in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (Section 2107.01 of the Manual of Patent Examining Procedure, 8th Edition, August 2001, under the heading I. Specific and Substantial Requirements, Research Tools):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

The PTO's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases, acknowledged by the PTO's Training Materials to be useful.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S.

Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What Applicants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

Such beneficial uses beyond studying the claimed invention itself have been demonstrated, in particular those described in the Furness Declaration. The Furness Declaration demonstrates that the claimed invention is a tool, rather than an object, of research, and exactly how that tool is used. Without the claimed invention, it would be more difficult to generate information regarding the properties of tissues, cells, drug candidates and toxins apart from additional information about the polypeptide itself.

The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility." These include: screening libraries of pharmaceutical agents to identify those which specifically bind NHT in a variety of drug screening techniques; generating antibodies which specifically bind and can identify NHT; and titration of NHT to initially determine the effective dose in cell culture assays or in animal models.

III. Applicants' evidence that the claimed invention is a member of the TUBBY protein family would be found by one skilled in the art to be more likely than not true

A. The similarity of the claimed polypeptide to another of undisputed utility demonstrates utility beyond the reasonable probability required by law.

Because there is a substantial likelihood that the claimed NHT shares homology with the TUBBY polypeptide family, a family in which the members have undisputed utility, homology can be used to show a substantial likelihood that the claimed polypeptide is similarly useful. Applicants need not show any more to demonstrate utility. Under the applicable law, once the applicant demonstrates a *prima facie* case of homology, the Examiner must accept the assertion

of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. *See In re Brana*, 51 F.3d at 1566-67; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974).

As indicated by the final Utility Examination Guidelines (66 FR 1092, January 5, 2001), where the asserted specific, substantial and credible utility for the claimed polypeptide/protein can be based upon homology to existing proteins having an accepted utility, "the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion." Applicants submit that this Office Action failed to provide sufficient evidence or sound reasoning to rebut Applicants' asserted use of the polypeptide.

In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967); *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973).

In fact, at a recent Biotechnology Customer Partnership Meeting held at the USPTO on April17, 2001, in a talk by Senior Examiner James Martinell, it was emphasized that Applicants' assertion that his claimed protein "is a member of a family of proteins that [is] already known based upon amino acid sequence homology" can be effective as an assertion of utility for the claimed sequence. According to Dr. Martinell, the proper question for the Examiner to ask, after searching the prior art for the claimed protein, is "Would one of skill in the art accept that the protein has been placed in the correct family of proteins as is asserted?" The "two" [sic: three] possible answers that can be deduced from this prior art search are, according to Dr. Martinell:

- The search does not reveal any **evidence** that the family attribution made in the application is either **incorrect or may be incorrect**
- The protein either **more likely belongs to a family other than that asserted** in the application or **likely does not belong to the family asserted** in the application
- The search shows that the attribution is likely correct

(From handouts of Dr. Martinell's slides distributed April 17, 2001; emphasis added)

This Office Action has failed to meet the above requirements now recognized by the USPTO. No evidence is cited particular to the claimed protein, e.g., inconsistent findings deduced from the search, upon which to base any objection to the assignment of functional homology to this family of TUBBY proteins. Indeed, there is no such evidence.

In this regard, NHT is homologous to two TUBBY polypeptides, one from mouse (SEQ ID NO:3) and one from human (SEQ ID NO:4). In particular, NHT shares more than 49% sequence identity over 491 amino acid residues, and is in fact nearly 70% identical with the two from about amino acid D187 to D436 (about 249 amino acid residues) (see specification, page 11, and Figures2 A and 2B).

This is more than enough homology to demonstrate a reasonable probability that the utility of the human TUBBY polypeptides can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et. al., Proc. Natl. Acad. Sci. 95:6073-78 (1998) (Reference No. 5). Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to the human TUBBY polypeptides is, accordingly, very high. Additional studies by others of the *TUB* gene family provide further evidence that NHT is a member of the TUBBY protein family.

Applicants submit the results of a recent BLASTP analysis of SEQ ID NO:1 verses the genpept database (NCBI, version 132). What is readily evident is that SEQ ID NO:1 has **99%** identity, from residue M1 to residue I439 to tubby-like protein 3 (TULP3, GI21618457), and from 49% to 93% sequence identity to nine additional proteins, all of which are either tubby proteins, TUB homologs, or tubby homologs from either human or mouse (Exhibit A). The tubby-like protein 3 has recently been shown to function in signal transduction from heterotrimeric G protein-coupled receptors (Santagata, S. *et al.* (2001) Science 292:2041-2050, Exhibit B). Clearly, this is credible, scientific evidence that one skilled in the art would more likely than not conclude that SEQ ID NO:1 as a member of the TUBBY protein family. Therefore, Applicants meet the standard of proof and the Office has failed to present evidence to the contrary refuting Applicants' findings.

It is undisputed that the claimed polypeptide is a protein having the sequence shown as SEQ ID NO:1 in the patent application and referred to as NHT in the application. Moreover, since there is a substantial likelihood that the claimed polypeptide is a member of the TUBBY polypeptide family, and the members are indisputably useful, there is by implication a substantial likelihood that the claimed polypeptide is similarly useful. Applicants need not show any more to demonstrate utility. Therefore, the Examiner must accept applicants' demonstration that the claimed polypeptide is a member of the TUBBY proteins and that the utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-1392, 183 USPQ 288 (CCPA 1974).

The final Utility Examination Guidelines further provides that

> [w]hen a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein.

This Office Action offers no evidence that the members of this class of TUBBY proteins do not share a specific, substantial functional attribute or utility, despite having structural features in common. Thus, this strongly indicates that any member of this TUBBY protein class would have some patentable utility. It follows that there is a more substantial likelihood that the claimed polypeptide also has a patentable utility, regardless of its actual function. The law has never required a patentee to prove more.

It appears from the statements of the Office Action that Applicants are being required to assert a rigorous correlation to establish the identity of NHT as a member of the TUBBY family as well as to establish a specific disease affected by NHT. However, the final Utility Examination Guidelines provides that

> [A] "rigorous correlation" need not be shown in order to establish practical utility; "reasonable correlation" is sufficient. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895, 1900 (Fed Cir. 1996).

The Examiner must accept the applicants' demonstration that the homology between the claimed invention and TUBBY polypeptides demonstrates utility by a reasonable probability, and additionally, that the claimed polypeptide is a member of the TUBBY polypeptide family unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

B. Membership in a Class of Useful Products Can Be Proof of Utility

Despite evidence that the claimed polypeptide is a member of the TUBBY polypeptide family, whose members indisputably are useful, the Examiner refused to impute the utility of the members of the TUBBY polypeptide family to NHT. In the Office Action of September 24, 2002, the Patent Examiner takes the position that, "[t]he assertion that the disclosed NHT has biological activities similar to known TUBBY cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities." (Office Action of September 24, 2002, page 3, ¶ 3). To demonstrate utility by membership in the class of TUBBY polypeptides, the Examiner would require that all TUBBY polypeptides possess a "common" utility.

The Examiner has not provided any evidence that any member of the TUBBY polypeptide family, let alone a substantial number of those members, is not useful. In such circumstances the only reasonable inference is that the claimed polypeptide must be, like the other members of the TUBBY polypeptide family, useful.

Even if the Examiner's "common utility" criterion were correct, the TUBBY polypeptide family would meet it. It is undisputed that known members of the TUBBY polypeptide family function in signal transduction from heterotrimeric G protein-coupled receptors. A person of ordinary skill in the art need not know any more about how the claimed invention functions in signal transduction from heterotrimeric G protein-coupled receptors to use it, and the Examiner presents no evidence to the contrary. Instead, the Examiner makes the conclusory observation

that a person of ordinary skill in the art would need to know whether, for example, any given TUBBY polypeptide functions in signal transduction from heterotrimeric G protein-coupled receptors. The Examiner then goes on to assume that the only use for NHT absent knowledge as to how this member of the TUBBY polypeptide family actually works is further study of NHT itself. However, this assumption is incorrect.

As disclosed by Applicants, knowledge that NHT is a TUBBY-like polypeptide is more than sufficient to make it useful for the diagnosis and treatment of appetite and eating disorders. Indeed, NHT has been shown to be expressed in brain, neuronal anc lymph node cDNA libraries. The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

C. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

Applicants have shown that NHT shares homology with the TUBBY polypeptide family, a family consisting of members known to have undisputed utility, and therefore, homology can be used to show a substantial likelihood that the claimed polypeptide is similarly useful. Applicants need not show any more to demonstrate utility. Specifically, the TUBBY family includes TULP3 which shares 99% sequence identity with NHT. TULP3 has been demonstrated to function in signal transduction from heterotrimeric G protein-coupled receptors. Based on the high level of sequence homology, structural characteristics and tissue expression, Applicants have demonstrated a *prima facie* case for homology as an acceptable assertion of utility of the claimed polypeptides. Such an assertion of utility would be determined to be sound scientific reasoning by one skilled in the art. Therefore, the Examiner must accept the applicants' demonstration by homology that the claimed polypeptide is a member of the TUBBY polypeptide family and that the homology between the claimed invention and TUBBY polypeptides demonstrates utility by a reasonable probability, unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility.

Under the applicable law, once the applicant demonstrates a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. *See In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974).

Moreover, as indicated by the final Utility Examination Guidelines (66 FR 1092, January 5, 2001), where the asserted specific, substantial and credible utility for the claimed polypeptide/protein can be based upon homology to existing proteins having an accepted utility, "the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion." Applicants submit that this Office Action failed to provide sufficient evidence or sound reasoning to rebut Applicants' asserted use of the polypeptide.

The literature cited by the Examiner *infra* is not inconsistent with the Applicants' proof of homology by a reasonable probability. It may show that Applicants cannot prove function by homology with **certainty**, but Applicants need not meet such a rigorous standard of proof. The literature cited identifies some of the difficulties involved in predicting biological activity, or membership in a protein family, though none suggest that functional homology cannot be inferred by a reasonable probability as in this case. The Examiner rejected the pending claims on the ground that the applicant cannot "credibly" impute utility to the claimed invention based on its 49% homology to another polypeptide undisputed by the Examiner to be useful. The Examiner's rejection is both incorrect as a matter of fact and as a matter of procedural law.

In the present case, the Office Action alleges that the amino acid sequence identity between NHT and known TUBBY proteins is insufficient to establish that NHT is a member of the TUBBY family of proteins because "[t]he assertion that the disclosed NHT has biological activities similar to known TUBBY cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities" (Office Action, filed September 24, 2002, page 3). The Examiner cites Tischer *et al.* (U.S.Patent 5,194,596), Benjamin *et al.* (1998), Vukicevic *et al.* (1996), North *et al.* (1997), Gu *et al.* (1998) and Hayes *et al.* (1998) as support to doubt Applicants asserted utility. Importantly, all of these documents

fail to support the outstanding rejections, and none contradict Brenner's basic rule that sequence homology in excess of 40% over 70 or more amino acid residues yields a high probability of functional homology as well. At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function or biological activity with certainty.

The Examiner cites Tischer *et al.* and Benjamin *et al.* as evidence that VEGF, though a member of the PDGF, or platelet-derived growth factor family, functions opposite PDGF. As evidenced *supra* NHT is a member of the TUBBY family, specifically a homolog of TULP3, and the biological activity of NHT would be understood by one of skill in the art to be associated with signal transduction. The Examiner further cited Vukecevic *et al.* as evidence that TGF-β can induce metanephrogenesis, but related superfamily members BMP-2 and TGF-β1 did not effect metanephrogenesis under identical conditions. Therefore, to accept the Examiner's premise that all proteins within a family have identical function, one would also have to accept that each protein can act "universally" on all cells, tissues or organs in which the protein is found. Such an assertion is neither scientifically accurate nor in evidence with respect to the teachings of Tischer *et al.*, Benjamin *et al.*, Vukicevic *et al.*, or the instant application. Therefore, Tischer *et al.*, Benjamin *et al.* and Vukicevic *et al.* do not support the Examiner's position because the biological activity of NHT does indeed correlate with that of other members of the TUBBY protein family. Applicants' assertion is only that SEQ ID NO:1 is a member of the TUBBY protein family.

Likewise, the Examiner's citation of North *et al.* and Gu *et al.* each of which teach TUBBY-related proteins associated with ocular disease, but not with appetite or eating disorders. Each publication, taken together or separately teach that as of 1998, the function of the *TUB* gene was undetermined, includes additional family members *TULP1* and *TULP2*, and comprises an evolutionarily conserved gene family. Gu *et al.* teach that additional members of the *tubby* gene family exhibit a more restricted pattern of expression. Thus, the expression and association of TULP1 and TULP2 with ocular disorders would be expected since this is where the proteins are expressed. This is not contrary to Applicants' assertion that as a result of both brain and neuronal tissue and lymph node tissue expression that NHT would likewise be found by one skilled in the art to reasonably expect that NHT would be involved in disorders involving

appetite or eating disorders, disorders understood to have a glandular and/or neural component. Such a hypothesis as this is in fact supported by the Santagata *et al.* paper. Therefore, although function cannot be assigned with certainty, Applicants' assertion that SEQ ID NO:1 is associated with appetite or eating disorders would be found to be more likely than not true by one skilled in the art.

The Examiner further cited Haynes *et al.* in support of the Examiner's assertion that nucleic acid levels are not predictive of protein levels. The Northern data presented by Applicants represents evaluation of human tissue expression patterns. The Haynes *et al.* conclusion is based on the yeast *Saccharomyces cerevisiae* growing at mid-log phase. Only 80 proteins were selected for evaluation, no where is it taught which proteins were selected or if NHT was one of the proteins evaluated. Therefore, the Haynes *et al.* paper does not teach the expression levels of SEQ ID NO:1 and does not teach away from Applicants' position that SEQ ID NO:1 was expressed in brain and neuronal tissues and in lymph node tissues. Additionally, the findings of Santagata *et al.* support Applicants' assertions that expression of SEQ ID NO:1 is predominately located in the brain. Thus, the Haynes *et al.* paper is not applicable to the instant invention. The Examiner has attempted to broadly apply a laundry list of citations which do not teach applicants' invention. These citations do not constitute either evidence or sound scientific reasoning to show that a person of ordinary skill in the art would reasonably doubt Applicants' invention lacked patentable utility.

The Office's attention is further directed to Brenner *et al.*, *supra* that teaches through exhaustive analysis of a data set of proteins with **known** structural and functional relationships and with **<90%** overall sequence identity, that 30% identity has been determined to be a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner *et al.*, pages 6073 and 6076.) As shown in the Figures and as discussed in the specification, SEQ ID NO:1 shares 49% identity with at least two known TUBBY proteins over at least 491 residues, and nearly 70% identity over 249 residues, vastly exceeding this threshold. Moreover, recent BLASTP analysis actually confirms that NHT is a homolog of TULP-3, sharing 99% sequence identity between the two proteins. Since these criteria are based on a data set of known homologous proteins with shared structural and functional features, one of

ordinary skill in the art would reasonably expect the polypeptides of the invention possess the evolutionarily conserved **structural and functional** characteristics of a TUBBY protein.

It is known in the art that natural selection acts to conserve protein function. Conversely, mutations that reduce or abolish protein function are usually eliminated by natural selection. Based on these central tenets of molecular evolution, applicants put forth that the amino acid differences among Applicants' polypeptide and the known TUBBY proteins, are likely to occur at positions of minimal functional importance, while residues that are conserved are likely those that are important for protein function. One of ordinary skill in the art would therefore conclude that, more likely than not, the level of conservation observed between Applicants' polypeptide and the two known human TUBBY proteins are indicative of a common function, and hence common utility, among these proteins.

The preponderance of evidence therefore does not support the Examiner's basis for the rejection of claims under 35 U.S.C. § 101. The only relevant evidence of record shows that a person of ordinary skill in the art would not doubt that the claimed polypeptide is in fact a member of the TUBBY family of proteins, which are known to have specific utility.

IV. The diagnosis and treatment of appetite and eating disorders are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. Additionally, these uses are explained, in detail, in the Furness Declaration, discussed *supra*. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

The specification teaches that NHT is a member of the TUBBY polypeptide family and that defects in *TUB* genes and in TUBBY expression have been found in maturity onset diabetes, insulin resistance, progressive retinal degeneration and hearing loss (see specification, page 2, lines 9-10). Applicants have presented evidence that the claimed invention would have the

utilities of TUBBY proteins, proteins which are known to be involved in appetite and eating disorders. Therefore, one of ordinary skill in the art would conclude that, more likely than not, that NHT would also have these uses. Thus, the claimed invention meets the utility requirements under 35 U.S.C. §§ 101 and 112, first paragraph.

V. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to withdraw the rejections. To the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities, which meet the statutory requirements, and "general" utilities, which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.").)

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § III.B. (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. See *supra* § III.B. Thus, the Training Materials cannot be applied consistently with the law.

VI. To the extent the rejection of the claimed invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be withdrawn.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Applicants respectfully submit that rejections for lack of utility, based *inter alia*, on an allegation of "lack of specificity," as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of

these prior cases, "like a nose of wax,"[1] to target rejections of claims to polypeptide and polynucleotide sequences, as well as to claims to methods of detecting said polynucleotide sequences, where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be withdrawn.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

Rejection under 35 U.S.C. §112, first paragraph, enablement

Claims 1, 2, 16 and 17 stand rejected under the first paragraph of 35 U.S.C. §112 for allegedly not providing an enabling specification, since, "the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." The Office continues, "even if it were found that the specification were enabling for a protein of SEQ ID NO:1, enablement would not be commensurate in scope with claims to proteins which comprise biologically o[r] immunogenically active fragments thereof, nor for naturally occurring proteins with 90% sequence identity to such. (Office Action of September 24, 2002, page 5).

Applicants traverse this rejection for the reasons submitted below.

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[1]"The concept of patentable subject matter under §101 is not 'like a nose of wax which may be turned and twisted in any direction * * *.' *White v. Dunbar*, 119 U.S. 47, 51." *(Parker v. Flook,* 198 USPQ 193 (US SupCt 1978))

At the outset, it should be noted that issues pertaining to "immunogenic fragments" of SEQ ID NO:1 are moot, since the recitation of immunogenic fragments of SEQ ID NO:1 was deleted from the claim 1 by the present amendments. Hence, the protein of SEQ ID NO:1, and the recited "variants" and "biologically-active fragments" of SEQ ID NO:1 are at issue here.

To fulfill the enablement requirement of 35 U.S.C. §112, first paragraph, the claimed invention must be described in the specification in such as way as to enable one skilled in the relevant art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is submitted that the Specification does reasonably provide an adequate written description to **enable** the protein of SEQ ID NO:1, and the recited "variants" and "biologically-active fragments" of SEQ ID NO:1 as "now" claimed at the time of the filing of this application.

The Examiner is well aware that the relative skill of those in the art is very high and the amount of direction or guidance needed to be disclosed in the Specification **to make** the protein of SEQ ID NO:1, and the recited "variants" and "biologically-active fragments" of SEQ ID NO:1 as "now" claimed is well within the grasp of one of skill in the art upon reading the specification. Claimed variants of SEQ ID NO:1 are defined in the Specification at, for example, at page 5, lines 9-17; page 11, lines 1-10 and lines 13-16. Polypeptide sequence variants are known by one of skill in the art to have amino acid substitutions which do not alter the function of the polypeptide. For example, a change of an amino acid residue to another at the extreme amino- or the carboxy-terminus of the sequence most likely will not alter the function of the polypeptide. The Specification defines specific structural domains related to TUBBY proteins at page 11, lines 1-10; and page 2, lines 5-8. In addition, the Santagata. *et al.* paper *infra*, teach that members of the TUBBY protein family each possess a characteristic "tubby domain" at the carboxy-terminus of about 260 amino acid residues and which binds DNA (Santagata *et al.* page 2041).

Moreover, the functionality of the claimed variants will have been established anyway, since ***naturally occurring*** variants are claimed. Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of NHT) and SEQ ID NO:2 (the polynucleotide sequence encoding NHT), one of skill in the art would be able to routinely obtain: i) a polypeptide comprising an amino acid sequence of SEQ ID NO:1, ii) a polypeptide comprising a

naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, said polypeptide retaining at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1, or iii) a biologically-active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, said polypeptide retaining at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1." As an additional example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. See, *e.g.*, page 32, lines 16-25; and Example IV at pages 39-40. Therefore, one skilled in the art need not make and test vast numbers of polypeptides that are based on the amino acid sequence of SEQ ID NO:1. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature.

Additionally, an assay for monitoring NHT activity is described in the Specification, for example, at pages 43-44, Example IX. Assays to determine functional activity are considered routine experimentation when identifying functional sequence variants. One of ordinary skill in the art would recognize polypeptide sequences which are variants having at least 90% amino acid identity to SEQ ID NO:1 or biologically active fragments of SEQ ID NO:1, as those polypeptides or fragments which, when assayed, have at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1. Accordingly, polypeptides comprising an amino acid sequence that is 90% identical to the amino acid sequence of SEQ ID NO:1 or biologically active fragments of SEQ ID NO:1 can easily be identified by one of skill in the art based on both the presence of functional and structural domains and by the assay, all disclosed in the Specification. Thus, one of skill in the art would understand upon reading the specification, how to make the protein of SEQ ID NO:1, and the recited "variants" and "biologically-active fragments" of SEQ ID NO:1.

According to the Examiner, the Specification does not provide sufficient guidance of how **to use** the protein of SEQ ID NO:1, and the recited "variants" and "biologically-active fragments" of SEQ ID NO:1. This alleged deficiency is based on the theory that a precise biological function of the claimed polypeptides must be described by the Specification. Such a

position, however, ignores that the claimed polypeptides, including the "variant" polypeptides, and "biologically-active" fragments of the polypeptide, can be **used** in toxicology testing, drug discovery and disease diagnosis through expression profiling, as discussed in detail above in connection with the "utility" rejection. No detailed knowledge of the biological function of the claimed polypeptides is needed for such uses.

Moreover, as presented in the argument in support of the utility of the protein of SEQ ID NO:1, and the recited "variants" and "biologically-active fragments" of SEQ ID NO:1, *supra*, applicants presented evidence which would be found by one of skill in the art more likely than not true that NHT is a member of the TUBBY polypeptide family, a family with known utility, and as such, NHT shares similar functions with other members of the TUBBY protein family. The specification teaches an assay for monitoring NHT activity *supra*, which "enables" one skilled in the art to know how to **use** the protein of SEQ ID NO:1, and the recited "variants" and "biologically-active fragments" of SEQ ID NO:1 in monitoring the activity of NHT in patients diagnosed with obesity and eating disorders.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present Specification would

enable one to make and use the protein of SEQ ID NO:1, and the recited "variants" and "biologically-active fragments" of SEQ ID NO:1. Hence, a *prima facie* case for non-enablement has not been established with respect to the protein of SEQ ID NO:1, and the recited "variants" and "biologically-active fragments" of SEQ ID NO:1.

Accordingly, for all the above reasons, the claimed subject matter is described in the Specification in such a way that one skilled in the art can make and/or use the claimed invention. Therefore, reconsideration and withdrawal of this rejection to the claims are respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph, written description

Claims 1 and 16 stand rejected under the first paragraph of 35 U.S.C. §112 for allegedly containing subject matter "not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

Applicants traverse this rejection for the reasons submitted below.

A. Legal Requirements

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be

> disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

B. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1.

The subject matter recited in amended claim 1 is adequately disclosed in the Specification given what is are conventional or well known to one skilled in the art.

Please note that claim 1 as amended no longer recites "immunogenic" fragments of SEQ ID NO:1 rendering this grounds of rejection moot. It is submitted that the Specification provides an adequate written description of the claimed variants of SEQ ID NO:1 to convey with reasonable clarity to those skilled in the art that applicants were in possession of the invention as "now" claimed at the time of the filing of this application.

Variants of SEQ ID NO:1 are defined in the Specification at, for example, page 5, lines 9-17; page 11, lines 1-10 and lines 13-16. Polypeptide sequence variants are know by one of skill in the art to have amino acid substitutions which do not alter the function of the polypeptide. For example, a change of an amino acid residue to another at the extreme amino- or the caroboxy-terminus of the sequence most likely will not alter the function of the polypeptide. The Specification defines specific structural domains related to NHT proteins at page page11, lines 1-10. Structural domains within NHT are two potential N-glycosylation sites at N_{162} and N_{352} and potential cAMP or cGMP phosphorylation sites at R_{241} and R_{319}. NHT has chemical and structural homology with the mouse and human tub genes (SEQ ID NO:3 and SEQ ID NO:4, respectively). In particular, NHT shares about 49% identity with the mouse and human tub proteins. Accordingly, it is well within the skill of those in this art to identity those polypeptides comprising an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1.

Additionally, an assay to measure NHT activity is defined in the specification at pages 43-44, Example IX. Assays to determine functional activity are considered routine experimentation when identifying functional sequence variants. Also, as taught by Santagata *et al.*, members of the TUBBY protein family each possess a characteristic "tubby domain" at the carboxy-terminus of about 260 amino acid residues and which binds DNA (Santagata *et al.* page 2041). One of ordinary skill in the art would recognize polypeptide sequences which are variants having at least 90% amino acid identity to SEQ ID NO:1, as those polypeptide sequences which, have NHT activity. Accordingly, polypeptides comprising a naturally-occurring amino acid sequence that is 90% identical to the amino acid sequence of SEQ ID NO:1 can easily be identified by one of skill in the art based on both the presence of functional and structural domains, all disclosed in the Specification. Accordingly, Applicants have disclosed the claimed invention in sufficient detail and provided identifying characteristics such that the skilled artisan would understand that Applicants were in possession of the claimed invention. Therefore, the specification provides an adequate written description of the claimed variants of SEQ ID NO:1 to convey with reasonable clarity to those skilled in the art that applicants were in possession of the invention as "now" claimed at the time of the filing of this application.

Moreover, the Office Action asserts at page 6 of the September 24, 2002 Office Action that the encompassed polypeptides, with the exception of SEQ ID NO:1, cannot be envisioned by the skilled artisan, and "therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation" and further that "[o]ne cannot describe what one has not conceived." Applicants respectfully remind the Office, that constructive reduction to practice has occurred regarding the instant application. Constructive reduction to practice, by the filing of the instant specification and its parent application, U.S. Serial No. 08/812,824 (hereinafter referred to as the "LaBrie '824 application"), filed March 6, 1997, to which priority is claimed, is evidence that Applicants had conceived" that which is claimed. See M.P.E.P. § 715.07. Therefore, contrary to the Office's assertion, Applicants did meet the requirements of both conception and reduction to practice of the instant invention as claimed. Accordingly, the Specification provides an adequate written description of the claimed polypeptide sequences to convey with reasonable clarity to those skilled in the art that Applicants were in possession of the invention as "now" claimed at the time of filing of this

application and the LaBrie '824 application. Therefore, Applicants respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. §112, second paragraph, for indefiniteness

Claims 1, 2, 16 and 17 were rejected as indefinite for allegedly "failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" and further that, "[i]t cannot be determined which 90% identical sequences are or are not naturally occurring" (Office Action of September 24, 2002, page 7). The Examiner stated that "[c]laim 16 is further indefinitie as it is not clear for what the excipient is to be acceptable, therefore, the metes and bounds of the claim cannot be determined," and [c]laims 2 and 17 are rejected for depending from an indefinite claim." (Office Action of September 24, 2002, page 7).

The standard for "definiteness" is that the claims define patentable subject matter with a reasonable degree of precision and particularity. See *In re Miller*, 169 USPQ 597, 599 (CCPA 1971); *In re Moore*, 169 USPQ 236, 238 (CCPA 1971). See also MPEP §706.03(d). In this regard, the Supreme Court has indicated that the primary purpose of claim language is to give "fair" notice of what would constitute the infringement of a claim. See *United Carbon Co. v. Binny & Smith Co.,* 317 U.S. 228, 55 USPQ 381 (1942). In other words, the basic purpose of 35 U.S.C. §112, second paragraph is to require a claim to reasonably apprize those skilled in the art of the scope of the invention defined by that claim and give fair notice of what constitutes infringement of the claim. See *Antonious v. Pro Group Inc.*, 217 USPQ 875, 877 (6th Cir. 1983).

One of skill in the art, when reading the Specification, would understand the meaning of the claims. "Naturally occurring" would be understood by one of skill in the art and even by an unskilled person of the art to be that which occurs in nature. Moreover, the Specification at page 11 describes the term "fragment" as meaning:

> The term "portion", as used herein, with regard to a protein (as in "a portion of a given protein") refers to fragments of that protein. The fragments may range in size from four amino acid residues to the entire amino acid sequence minus one amino acid. Thus, a protein "comprising at least a portion of the amino acid sequence of SEQ ID NO:1" encompasses the full-length human NHT and fragments thereof. (Specification, page 8, lines 21-25)

When interpreting the claims in light of the specification, claim 1 b) claims "a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." Therefore, the entire length of SEQ ID NO:1. Thus, claim 1 would be understood by one of skill in the art to encompass protein homologs which have chemical and structural similarity to the polypeptide of SEQ ID NO:1 which are at least 90% identical to the polypeptide sequence of SEQ ID NO:1.

Hence, the meaning of the claims is clear. The Examiner has asserted that the claims are indefinite because it is not clear "which 90% identical sequences are or are not naturally occurring." As presented by Applicants, interpretation of a "naturally occurring amino acid sequence" is provided within the Specification, see for example pages 4-5 in which an amino acid sequence which is "natural" is not "synthetic, semi-synthetic, or recombinant." Thus, withdrawal of this rejection is therefore requested.

Rejection of Claims 1 and 16 under 35 U.S.C. §102 (e)

Although not acquiescing in the stated reason for the rejections of claims 1 and 16, claim 1 has been amended, adding, "said polypeptide retaining at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1" and removing recitation of "immunogenic fragments." Kleyn *et al.* do not teach a polypeptide comprising SEQ ID NO:1 or biologically-active fragments of SEQ ID NO:1, therefore, claims 1 and 16 are not anticipated by Kleyn *et al.* and withdrawal of this rejection is requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Agent at (650) 621-8555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

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Date: 13, December 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The first paragraph beginning of page 1 has been amended as follows:

This application is a divisional application of U.S. application Serial Number 08/812,824, filed March 6, 1997, now U.S. Patent No. 6,204,372, the contents of which are hereby incorporated by reference.

IN THE CLAIMS:

Claims 1 and 16 have been amended as follows:

1. (Twice Amended) An isolated polypeptide selected from the group consisting of:

a) a polypeptide comprising an amino acid sequence of SEQ ID NO:1,

b) a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, said polypeptide retaining at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1, and

c) a biologically-active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, said polypeptide retaining at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1[, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1].

16. (Once Amended) A composition comprising a polypeptide of claim 1 [and acceptable excipient].